

REMARKS

I. Status of the Claims

Claims 1-85, 87-92 and 100 were pending. Claims 4-8, 10, 62-69, 71, 77, 79-85 , 87-92 and 100 were withdrawn from consideration and claims 1-3, 9, 11-61, 70, 72-76 and 78 were rejected. The present response amends claims 1, 73, 74, 78-80, 82 and cancels claims 6-11, 15, 67-72, 75-77 without prejudice.

Upon entry of the amendments, claims 1-4, 12-14, 16-66, 73, 74, 76-85, 87-92 and 100 will be pending.

II. Description of the Amendments

Claim 1 has been amended to:

- amend the definition of D by deleting the options O, S, S(O) and S(O)₂;
- delete the options for V other than the option "V is absent" as recited in original claim 11;
- amend the definition of W by deleting the options S, S(O) and S(O)₂;
- limit V, by incorporating the limitations of original PCT claim 11;
- limit W, by incorporating the limitations of original PCT claims 2 and 5;
- amend the definition of Z, by replacing the first definition with two narrower definitions at page 38, lines 8-12 and line 13-15 of the description as originally filed;
- amend the definition of R¹, by replacing the first definition with the narrower definition at page 39, lines 13-14 of the description as originally filed; and
- limit R², by replacing the first definition with the definition of original claims 17 (excluding the alternative, H) and 20.

Claim 17 was amended to delete the alternative H to conform to new claim 1.

Claim 73 was amended to delete those species not encompassed by new claim 1 and to add compound 1-[5-nitro-6-(4-trifluoromethylsulfanyl-phenoxy)-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester (A155) which appears at page 66 of the description.

Claim 74 and has been amended to delete those species no longer encompassed by new claim 1 and to add compound 4-[4-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-1-yl]-6-(4-methylsulfanyl-phenylamino)-pyrimidine-5-carbonitrile (B99) which appears at page 80 of the description.

Claims 78, 79, 82 and 100 were amended to delete the term "agonist".

Claim 80 was amended to insert correct the term "diabetes"; see, for example, page 91, lines 18-19.

Claims 6-11, 15, 67-72, 75-77 have been cancelled.

Any claims or subject matter cancelled has been cancelled without disclaimer or prejudice. Applicants fully reserve the right to reinstate such subject matter in the present application or pursue the cancelled subject matter in a continuing application.

III. Response to the Office Action

A. Restriction Requirement

The Office maintained the restriction requirement. The applicants elected Group V, which was defined as follows. The applicants have amended the claims to conform the definitions of X, Y, and V to those of the elected Group. The applicants are filing a petition from the restriction requirement herewith. Insofar as claim 1 continues to encompass more than one of the Groups defined by in the Restriction Requirement, the inclusion of such non-elected claim subject matter in the claim is not believed to be improper and, as discussed below, should be treated according to the procedure set forth in MPEP 803.02 (Markush Claims) and 809 (Linking Claims).

B. Objections to the Specification

1. Abstract of the Disclosure

The Office Action states:

Applicant is reminded of the proper content of an Abstract of the Disclosure. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, e.g., "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as

oral antidiabetics." ... Complete revision of the content of the abstract is required on a separate sheet.

Applicants have entered an amendment to enter the Abstract of the Disclosure, providing the same on a separate sheet.

The text of the abstract provided corresponds to the text of the abstract which was provided in the International Application. The text describes the general nature of the compounds and their use. While the Office states that "revision of the content of the abstract is required", it is noted that the Office Action does not indicate that there were any deficiencies in the abstract provided with the International Application.

It is respectfully submitted that the Abstract of the Disclosure meets the requirements of a proper Abstract of the Disclosure as set forth in the Office Action and also as described in the MPEP. It is therefore requested that the Objection be withdrawn. If the Office continues to consider that the Abstract is deficient, the applicants would sincerely appreciate the Examiner's suggestions for revisions to the Abstract which would address any such supposed deficiencies.

C. Objection to the Drawings

The Office Action states that:

The informal drawings are not of sufficient quality to permit examination. Accordingly, replacement drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to this Office action. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. Presently, Figured 4D is missing the legend for the X axis of the graphical illustration.

Applicant is given a TWO MONTH time period to submit new drawings in compliance with 37 CFR 1.81. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a). Failure to timely submit replacement drawing sheets will result in ABANDONMENT of the application.

The applicants are providing a corrected drawing sheet herewith.

The applicants note that the above-referenced paragraph states a **two month period** for providing corrected drawings, which is inconsistent with the **three month shortened statutory period** for response stated on the Office Action Summary.

MPEP 710.02(a) states that "[a]n indication of a shortened time for reply should appear prominently on the first page of all copies of actions in which a shortened time for reply has been set so that a person merely scanning the action can easily see it" and MPEP 710.02(b) states that **a three month shortened statutory period should be provided for replying to an Office Action.**

In view of the foregoing passages quoted from the MPEP **applicants assume that the three month shortened statutory period** was intended to apply to the response to the present Office Action since the Office Action is an Office Action on the merits and a three month shortened statutory period was prominently displayed on the Office Action Summary.

Applicants further assume that the indication of a two month period for providing new drawings was given in error due to the inappropriate use of Form Paragraph 6.26. The Examiner Notes to Form Paragraph 6.26 (see MPEP 608.02(b)) – the Form Paragraph used by the Office to Object to the drawings – indicate that "**[u]se of this form paragraph should be extremely rare and limited to those instances where no examination can be performed due to the poor quality of the drawings** resulting in a lack of understanding of the claimed subject matter." Since the Examiner issued a complete Office Action on the merits, it is apparent that the Examiner was able to examine the application – and apparently was able to understand the claimed subject matter – despite any supposed deficiency with the drawings, so Form Paragraph 6.26 was not appropriately used.

Accordingly, in calculating the period for reply to the Office Action, and for providing corrected drawings, applicants have assumed that the three month shortened statutory period which was indicated prominently on the Office Action Summary was the applicable period.

If, however, applicants are mistaken, and the two month period was indeed intended to apply, the Commissioner is authorized to treat this reply as a constructive petition for an

additional month's extension of time, and to apply the appropriate fee to the applicants' representative's Deposit Account.

D. Objection to the Claims

The Office Action objects to claims 1-78 for allegedly containing non-elected subject matter, and states that other claims do not include any elected subject matter. Applicants traverse the objection as being improper to the extent that the restriction requirement is improper. Applicants also traverse the objection because it is not improper for a claim to encompass non-elected subject matter, and therefore no "correction" is required, as the Office Action states. Rather, the claim should be treated according to the procedure set forth in MPEP 803.02 (Markush Claims) and 809 (Linking Claims).

MPEP 803.02 sets forth a procedure which may be followed allowing restriction of Markush claims, under which an examiner may make a *provisional* restriction requirement (an election of species requirement), which is given effect if the Markush claim (examined as to the elected species) is found not allowable. The procedure requires that if the Examiner finds that the claim *is* allowable as to the elected species, then the examination must be extended to encompass non-elected species.

Furthermore, the present application contains linking claims. For example, at least claim 1 is a linking claim linking the allegedly distinct inventions encompassed by Groups I-XIII. The MPEP states that "the linking claims must be examined with, and thus are considered part of, the invention elected." Any restriction requirement as to the linked inventions should be withdrawn upon an indication of the allowability of the linking claim(s). *See* MPEP 809.03.

While the Office's rules provide for the Office to insist that a claim which is drawn to a non-elected invention, and which is not eligible for rejoinder, to be cancelled, there is no provision in the Office's rules or the MPEP for the Office to insist that *part of a claim* be cancelled as being drawn to non-elected subject matter. There is therefore no basis for an objection to, for example, claim 1 for "containing non-elected subject matter": claim 1 is a linking claim and is therefore elected. If the Examiner believes the applicants are incorrect, the applicants request that the particular provision of the MPEP or CFR being relied upon be pointed

out. The applicants refer the Examiner to the provisions of 803.02 and 809 quoted above, which explain that a linking claim is included with the elected group and that where a claim is broader than an initially-made restriction requirement examination must be extended to the extent necessary to determine patentability.

E. Claim Rejections

1. Rejection of Claims 1-3, 9, 11-61, 70, 72-76 and 78 under the Enablement Requirement of 35 U.S.C. § 112, First Paragraph

Claims 1-3, 9, 11-61, 70, 72-76 and 78 were rejected under the Enablement Requirement of 35 U.S.C. § 112, first paragraph. The Office Action acknowledges that the claims are enabled for a pyrimidine when R¹ is hydrogen, N-A-B-D is a piperidinyl ring, Ar¹ is a phenyl or benzyl ring. It is stated that "the specification ... does not reasonably provide enablement for all of the other groups listed nor any hydrates or solvates within the broad Claim 1. The applicants respectfully request reconsideration of the rejection.

The Office is respectfully reminded that applicants enjoy a **presumption** that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. § 112. MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)). Under the presumption, the **enablement requirement must be considered to be satisfied unless and until there is a reason to doubt the objective truth of the specification**, and the initial burden of establishing a basis for denying patentability to a claimed invention therefore rests upon the examiner. *Id.* See also *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988); *In re Thorpe*, 777 F.2d 695 (Fed. Cir. 1985); *In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984). "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable **evidence or reasoning which is inconsistent with the contested statement**. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)).

An application satisfies the enablement requirement if the disclosure has sufficient information to enable the person skilled in the pertinent art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test for whether experimentation would be undue is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine. *Id* at 737. The fact that experimentation may be required and may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. on other grounds sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976).

The question as to whether the application enables the person of ordinary skill in the art to make the compounds of the invention is whether he can do so without undue experimentation, using the disclosure of the application, the knowledge of one of ordinary skill in the art, and applying an ordinary level of creativity to the problem. It is not necessary for "a patent specification to become a catalogue of existing technology", and "[a] patent specification need not teach, and preferably omits, what is well known in the art." MPEP 2182 (citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)). Furthermore, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742 (2007). The Office fails to provide reasoning or analysis sufficient to raise a *bona fide* issue that the claims of the present application lack enablement.

The applicants point out that the claims have been tailored significantly from those which were previously pending in the application, and that, in particular, the claims have been amended to recite a compound wherein the ring containing X and Y is a pyrimidine and the scope of the substitutents R¹, Ar¹-V-W-, Z and the ring N-A-B-D have been narrowed. The claims are amply enabled by the extensive description provided in the specification.

While the reasoning that the Office provides in support of the rejection is very unclear, it appears from the reasons given that the Office doubts:

- (1) whether the person skilled in the art could make compounds corresponding to the full scope of the claims; and
- (2) whether the person skilled in the art could make solvates and/or hydrates of the compounds.

The applicants respectfully submit that the rejection must be withdrawn for at least the following reasons:

a. **The Reasons Given For the Rejection Do Not Appear to Relate to the Disclosure of the Present Application.**

The Office discusses the guidance provided by the applicants in the specification, one of the factors identified in *Wands*, and surely a factor that must be considered in properly assessing enablement. However, it is apparent from the reasons given in support of the rejection by the Office that **the Examiner has considered and based the rejection on the specification and claims of a different application from that presently pending.** As a result, the applicants respectfully submit the rejection surely must be withdrawn.

The Office Action states:

(1) Amount of guidance provided by Applicant. The Applicant has demonstrated within the application how to make triazolopyrimidines and pyrazolopyrimidines. However, there is no working example of any compounds with R groups other than previously mentioned nor has applicant demonstrated any N-oxides, prodrugs, polymorphs or formulations.

The applicants respectfully point out that the specification of the present application claims and describes how to make 1,2,3-trisubstituted aromatic compounds of the Formula Ia as described in claim 1.

The specification of the present application is not directed to "triazolopyrimidines and pyrazolopyrimidines", as discussed in the enablement rejection, there is no group "R" in the claims, nor do the claims mention the terms "N-oxides", "prodrugs", "polymorphs" or "formulations".

While the applicants do not disclaim triazolopyrimidines, pyrazolopyrimidines, N-oxides, prodrugs, polymorphs or formulations, to the extent that such compounds and compositions might fall within the scope of the claims, the applicants do not see how these reasons given for the rejection can have been derived from a proper consideration of the disclosure and claims of the present application. Rather, the remarks appear to refer to a different application, having a different specification (one apparently that describes triazolopyrimidines and pyrazolopyrimidines) and different claims from those at issue in the present application.

Respectfully, the applicants submit that any reasons given in support of the rejection of the claims of the present application should discuss what the specification of the **present application** discloses (or fails to disclose).

Given that the Office Action's rejection discusses the specification as describing the synthesis of compounds ("triazolopyrimidines and pyrazolopyrimidines") that are different from those actually described and claimed in the present application, it is not seen that the Office has presented any evidence or reasoning **inconsistent with** the enablement of the claims that ought to be under consideration in the **present application**. Thus, the Office has not provided any evidence or reasoning sufficient to overcome the presumption of enablement to which the applicants are entitled. The applicants note that the Office has, in fact, failed to provide any substantial evidence at all supporting the assertion that the person skilled in the art would not be able to make the claimed invention.

b. Compound Scope

The Office alleges that the examples provided in the specification are insufficient to support enablement of the full scope of the compound claims as defined in former claim 1.

As is noted above, the scope of the claimed compounds has been narrowed significantly from those which were considered when making the rejection. The applicants hope that the amendment will overcome the Office's concerns with regard to this issue.

The primary factor underlying the Office's conclusion that the specification did not adequately enable the full scope of the claims appears to be that the applicants have allegedly not

provided working examples of each and every one of the options provided for by the Markush formula of claim 1. For Example, the Office Action states:

3) *Number of working examples.* The compound core depicted with specific substituents represents a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any compounds, compositions or pharmaceutically acceptable salts where the R variables were not those mentioned above in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. Markush claims must be provided with support in the disclosure for each member of the Markush group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01 (p).

Applicants respectfully point out the requirement that "Markush claims must be provided with support in the disclosure for each member of the Markush group" requires does not require that the specification provide working examples of using all the substituent options. *See Ex Parte Hinze*, Appeal No. 2008-5635, slip op. at 7-8 (Bd. Pat. App. & Int., Jan. 29, 2009). (reversing an enablement rejection made on the grounds, *inter alia*, that not all substituent options were exemplified and stating that "the question is whether the Specification gave sufficient guidance to make and use compounds having the listed substituents, not whether working examples using all the substituents were provided.")

Applicants also respectfully point out that the present application provides a substantial amount of guidance on how to make compounds of the present claims. In addition to a general Scheme provided in drawing sheet 6, the specification on pages 127 to 222 describes in detail methods for making the compounds – including detailed instructions for synthesizing **over 300 Working Examples.**

Furthermore, although the applicants are not required to provide working examples for every possible substituent option, the scope of the working examples provided clearly goes beyond the scope that the Office has been willing to acknowledge to date as being enabled. For

example, while the Office acknowledges that compounds with Ar¹ as phenyl, N-A-B-D as a piperidinyl ring and R¹ as hydrogen, the scope of exemplification of these moieties is broader. For example, the examples are not limited to Ar¹ as phenyl (see, e.g., Examples A1, A2, A4, A67, A7, A8, A9, A10, A11, A12, A13, A14, A15, A19, A20, A21, A22, A25, A27, A31, A49, A66, A67, A68, A69, A70, A71, A72, A73, A78, A79, A94, A95, A96, A97, A98, A99, A105, A106, A125, A126, A128, A148, A163, B1, B18, B26, B27, B18, B19, B20, B32, B33, B34, B35, B37, B38, B79, B83, B100, B101, B103, B108, B127, B129, B134, B135, B136, B137, B139, C4, C7, C12, C15, C16, C17, C19, and E1), N-A-B-D as piperidine (see, e.g., Examples A9, A10, A63, A64, A65, A97 and B92) and R¹ as hydrogen (see, e.g. Examples A8, A164) or with the examples going beyond the scope that the Office acknowledges as being enabled with respect to each of R¹, N-A-B-D and Ar¹.

The Office also relies on an assertion that “chemistry is unpredictable” to support the rejection. A lengthy quote from Dörwald is provided as supposed evidence therefore. Yet the Office's consideration of the predictability factor is so generalized as to be irrelevant. It is patently not true that all chemistry is unpredictable: the reaction of an acid with a base, or the reaction of an alkali metal with water, for example, are entirely predictable. What is required for a proper consideration of the influence of the level of predictability in the art on the issue of enablement is not a broad general statement whether the field of chemistry as a whole is predictable, but analysis whether the results of experiments that would be required to carry out the synthesis of compounds of the invention would be reasonably predictable. The Office has not provided any reasoning establishing that the success of the synthetic reactions required to form the compounds of Formula I would be particularly unpredictable. Applicants' success in making hundreds of examples of such compounds suggests that the relevant chemistry is not, in fact, at all unpredictable. The question of whether the chemistry that would be required to carry out the synthesis of compounds of the invention would be predictable does not seem to have been considered by the Office.

Dörwald's statements are not relevant to the issue of the predictability of the chemistry required to make the compounds of the rejected claims. Dörwald makes general comments

which have no particular pertinence to the issue of whether the person skilled in the art would be able to make the compounds presently claimed in this application. Indeed, Dörwald fails to establish the proposition for which it is cited by the Office, i.e. that synthetic organic chemistry is inherently unpredictable. The section of Dörwald quoted by the Office recites that "most organic chemistry textbooks and research articles ... give the impression that organic chemical reactions proceed smoothly", so according to Dörwald *most* textbooks and research articles indicate that the practice of organic synthesis is quite predictable. Dörwald describes that unexpected difficulties are often encountered in the syntheses of "structurally complex natural products" but this does not provide any basis for concluding that undue experimentation would be required to make applicants' compounds because applicants' compounds are not "structurally complex natural products". Dörwald's observations that problems might be encountered in complex syntheses, such as the synthesis of complex natural products, is not inconsistent with his characterization of the organic chemical literature in general as describing that "organic chemical reactions proceed smoothly."

The applicants respectfully submit that the disclosure of the present application more than adequately supports enablement of the full scope of the compounds encompassed by Formula Ia of claim 1.

c. **Hydrates and other Solvates**

The Office alleges that the examples provided do not reasonably enable the synthesis of solvates of the claimed compounds. The applicants respectfully disagree.

The Vippagunta reference cited as evidence that the person skilled in the art would not be able to make solvates of the claimed compounds does not support the Office's position – and, in fact, strongly suggests that the person skilled in the art **would** be able to make such compounds. On page 15 col. 1 of Vippagunta, in his first remark introducing solvates and hydrates, Vippagunta states: "[i]t has been estimated that approximately **one-third of pharmaceutically active substances are capable of forming crystalline hydrates.**"

Far from emphasizing the difficulty of making solvates and hydrates, Vippagunta emphasizes their ubiquity. Applicants have provided hundreds of examples of pharmaceutically

active compounds of the claimed invention, and the Office characterizes the claims as encompassing “millions of compounds”. It is reasonable to believe that many of the compounds according to the invention can form solvates and hydrates.

Importantly, enablement is to be presumed as a matter of law, absent contrary evidence, and the Office has not presented any evidence whatsoever showing that solvates of compounds of the invention could not be formed. Thus, the Office has provided no basis for shifting the burden to the applicants to prove enablement of the claims.

The situation presented here is therefore quite unlike the situation which was presented in *Morton Intern. Inc. v. Cardinal Chemical Co.*, 5 F.3d 1464 (Fed. Cir. 1993), which the Office Action quotes out of context to suggest that it is proper to require that applicants prove the enablement their claims. In the *Moreton* case, the finding of lack of enablement was supported by “considerable evidence showing that those skilled in the art could not make the claimed compounds using the procedures of the specification” sufficient to shift the burden of showing enablement to the patentee. *Id.* at 1469-70. Here, the Office has provided no evidence whatsoever to show that the person skilled in the art would not be able to make compounds of the invention, so the citation to *Moreton* is inapposite.

Even if the specification does not explicitly describe working examples in the form of solvates, it is important to realize that this does provide any indication or evidence that the compounds are not capable of forming solvates since the methods usually used for purification of compounds in drug discovery (typically flash chromatography followed by evaporation of the product-containing fractions under reduced pressure) do not involve crystallization under the conditions which would form solvates.

As the applicant pointed out above, an application satisfies the enablement requirement if the disclosure has sufficient information to enable the person skilled in the pertinent art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). “The key word is ‘undue’ not ‘experimentation.’” *Id.* “Enablement is not precluded by the necessity for some experimentation such as routine screening.” *Id.* at 736-7.

It appears from the reasons given for the rejection that the Examiner appears to contend, citing Vippagunta that formation of crystalline solvates is somewhat unpredictable, particularly with regard to the number of molecules of water or solvent incorporated into the crystal lattice of a compound. The Office states:

"Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates." Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

Vippagunta's remarks focus largely on the difficulty of predicting the structure and stability of solvates (e.g. "the number of molecules of water or solvent"). The claims, however, do not recite having a particular number of solvent atoms, or a particular structural lattice. The applicants' claims, in fact, do not recite any particular features of hydrates and solvates that they encompass. Rather, the claims include all forms of the compounds defined in claim 1, including any hydrate or solvate. Even if solvate formation were somewhat unpredictable, as the Examiner contends, the claims would still satisfy the enablement requirement because such experimentation as might be required to prepare salts or hydrates of the compounds of the invention would be routine and well within the capacity of the skilled artisan, and would therefore not be undue, as is demonstrated by the references cited below.

The Office Action couches its discussion of issue of enablement in terms of the factors considered in *Wands*. It would therefore be instructive to compare the complex, unpredictable antibody technology described in *Wands* with the simple problem of making solvates and hydrates which the Office makes an issue in the present application.

The issue in *Wands* was whether the patentee had adequately enabled one skilled in the art to make certain high-affinity IgM antibodies. *Wands*, 858 F.2d at 735. The PTO had rejected the claims, stating that the production antibodies was unpredictable and unreliable, thus requiring

undue experimentation. *Id.* However, the Federal Circuit reversed, finding the claims to be enabled as a matter of law. The court made the point that even though the screening required to produce the antibodies was labor-intensive with a lot of steps (e.g., immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells, cloning the hybridoma, screening the resulting antibodies, etc.), all the methods needed to practice the invention were well known, and the amount of effort was not excessive enough to be undue *despite any unpredictability associated with making antibodies.* *Id* at 740.

In stark contrast to the complex and unpredictable antibody-making procedures at issue in *Wands*, the preparation of hydrates and solvates of a given organic molecule is substantially easier, overwhelmingly simpler, requires significantly fewer steps, and demands much less time than for the preparation of a monoclonal antibody. Accordingly, since the court concluded that the preparation of a monoclonal antibody was enabled *as a matter of law* despite the complex and lengthy process involved, it is unreasonable for the patent office to reject hydrates and solvates as lacking enablement given that they are infinitely simpler to make. The table below provides a step-by-step comparison of some of the major steps involved in the production of a monoclonal antibody (as disclosed in *In re Wands*) and the one step involved in making a hydrate or solvate. The experimentation involved in the production of a monoclonal antibody is tremendously more complex and time-consuming than forming a solvate, yet the court concluded that it was not excessive and undue.

Step	Monoclonal Antibody	Solvate or hydrate
1	immunize animal	Expose the compound to solvent or water
2	remove the spleen from the immunized animal	
3	separate the lymphocytes from the other spleen cells	
4	mix the lymphocytes with myeloma cells	
5	treat the mixture to cause fusion between the lymphocytes and the myeloma cells to make hybridomas that hopefully secrete the desired antibody	
6	separate the hybridoma cells from the unfused lymphocytes and myeloma cells by culturing in a medium in which only hybridoma cells survive	
7	culture single hybridoma cells (often 100 of different cells) in separate chambers	
8	assay the antibody secreted from each hybridoma culture to determine if it binds to the antigen	
Total Time	Months	About 1-2 days

Thus, to say the rejection of the claims based upon an assertion that the preparation of solvates would require "undue" experimentation is clearly inconsistent with the Federal Circuit's holding finding that the claims to forming antibodies were enabled as a matter of law in *Wands*.

Although making monoclonal antibodies involves a greater amount and complexity of experimentation than is involved in forming solvates, the preparations of monoclonal antibodies and solvates share the characteristic that the step(s) involved are well known and routine.

Applicants provide herewith evidence that solvate is easy, simple, requires few steps, and demands little time, and that the person of skill in the art routinely engages in such experimentation, and that the techniques for performing such experimentation are well known.

To make hydrates and solvates, samples of the organic compound are simply exposed to water or various different solvents. Exposure of the organic compounds to water and various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurring and/or crystallizing the samples from water or

solvent. In fact, it is difficult to conceive of a scientific method that is simpler to perform than placing a powder on a dish and letting it sit out on a humid day. Other typical procedures for making and identifying hydrates and solvates are described on pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999, a copy of which is provided herewith.

Once solvates are formed, they can be readily analyzed by routine methods. Examples of such techniques include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Karl Fischer titrimetry, X-ray diffractions (single crystal or powder), infrared spectroscopy (IR), polarized light microscopy, and hot stage microscopy or other routine techniques to detect and quantify the presence of solvate molecules in the sample. As evidence thereof, see page 18, right column, Vippagunta et al., which has been cited by the Office.

While there may be many solvents and conditions to try, the screen merely uses methods that are very well known in the art and considered quite simple. In fact, the process is *so* routine as to be amenable to high throughput screening, for example high throughput crystallization as described, for example, in Morissette, et al., *Adv. Drug Delivery Rev.*, 2004, 56, 275-300, a copy of which is provided herewith.

The Office Action attempts to base its enablement rejection solely on the alleged unpredictability of solvate formation and the fact that no specific examples of solvates have been described in the specification. *Wands* establishes that unpredictability (which was the main grounds of improper enablement rejection in *Wands*), even if it were established, is not dispositive. Also, there is no requirement for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 U.S.P.Q. 79 (Pat. Off. Bd. App. 1986). Given that one skilled in the art could make and identify various hydrates and solvates of a particular organic molecule using the routine screening methods discussed above, no working example is necessary to enable the invention. *Wands*, in fact, mandated that numerous factors be considered in evaluating enablement rather than the narrow approach taken by the Office here.

It is respectfully submitted that any unpredictability or the absence of examples of solvates specifically described as solvates or hydrates should be found to be clearly outweighed by the other factors considered in *Wands*.

d. The Reasons Given For the Rejection Do Not Consider the *Wands* Factors Together.

The Office Action correctly points out that under *Wands*, a conclusion of lack of enablement is to be reached not based upon consideration of a single factor, but a combination of factors.

In rejecting the claims here, the Office makes the same error that the Court of Appeals for the Federal Circuit was required to reverse in *Wands*. The Office has inappropriately made rejection for lack of enablement without taking proper account of **all the relevant factors**. While the reasons given for the rejection consider (albeit incompletely) several of the factors discussed in *Wands*, the Office Action unduly emphasizes certain factors while disregarding others, and fails to indicate how certain factors were considered to outweigh others in reaching the conclusion that the claims lacked adequate enablement. For example, the Office emphasizes supposed unpredictability in the art as a factor supporting enablement. However, the Office also indicates that the level of skill in the art is high. The Office fails altogether to consider the state of the prior art (e.g. the known, routine methods for preparing and screening solvates, for example). The Office does not explain why the factor of unpredictability, even if present, should outweigh all the other factors in reaching the conclusion of non-enablement.

e. Properly Considering the *Wands* Factors Together Should Lead to a Conclusion That The Claims are Adequately Enabled.

The applicants believe that a careful consideration of the relevant factors under *Wands* that it should be found that the applicants' specification provides a more than adequate description of how to make the invention, and that the Office has erred in its evaluation of these factors:

i. Breadth of the Claims.

The Office characterizes the claims as broad because they allegedly encompass "millions of compounds". However, the number of possible embodiments is not necessarily indicative of an unduly broad claim: even the narrowest and simplest of claims may be susceptible of many possible variations such that it compasses thousands, millions, or even an infinite number of possible embodiments. The Office's characterization disregards the **close structural relationship between the compounds encompassed by the claims**, in particular the analogous chemical functionalities of the compounds within the scope of the formula which would permit analogous routes to be used in preparing such compounds. As amended, the claims are directed to a narrow class of 4,5,6-trisubstituted pyrimidines. Many diverse compounds according to the invention could be synthesized from the same common intermediates, as is shown, for example by the synthetic scheme shown in Figure 6.

The person skilled in the art of medicinal chemistry will be familiar with the concept of combinatorial chemistry, or "multiple parallel synthesis" in which multiple analogous compounds can be synthesized in parallel by routine chemical manipulations to make "chemical libraries" of compounds, which can contain hundreds or thousands of compounds at a time, particularly when the compounds are closely structurally related as in the present application. Thus, the fact that a number of compounds might be encompassed by a claim would not necessarily indicate that the compounds would require an excessive amount of experimentation to prepare (assuming there would be a reason synthesis of more examples were required).

Due to the close structural relationship of the compounds claimed, the narrow breadth of the claims as amended is a factor which clearly supports enablement.

ii. The Level of Skill in the Art.

The Office states that the "artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience."

It appears, therefore that the Office is asserting that the level of skill in the art is high. Thus, this factor also supports a conclusion of enablement.

iii. Nature of the invention.

The Office characterizes the claims as being directed to "certain 1,2,3-trisubstituted aryl and heteroaryl derivatives that are modulators of glucose metabolism... useful in the prophylaxis or treatment of metabolic disorders and complications thereof, such as, diabetes and obesity." The claims under consideration are directed to organic chemical compounds for medicinal use.

Given that the Examiner has already acknowledged the high level of sophistication of the person skilled in the art of organic and medicinal chemistry, the nature of the invention is a factor that clearly supports enablement.

iv. The Level of Predictability in the Art.

The Office emphasizes the supposed unpredictability of the art, which appears to be the main reason in support of the rejection.

With respect to the synthesis of compounds applicants respectfully disagree that there is any evidence that the reactions and synthetic schemes required to prepare compounds according to the invention is unpredictable. The applicants have shown the synthesis of about 300 examples of compounds which are within the scope of the claims (or similar to such compounds) in the application.

As noted above, the quotation from Dörwald cited as evidence that "chemistry is unpredictable" does not relate to the chemical reactions required to synthesize compounds of the invention, and the reference does not state that chemistry generally is unpredictable. Dörwald describes that the "most organic chemistry textbooks and research articles" teach "that organic chemical reactions proceed smoothly", indicating that *most* textbooks and research articles indicate that the practice of organic synthesis is quite predictable. Dörwald's observations concerning the unpredictability that may be encountered in the syntheses of "structurally complex natural products" does not provide any basis for concluding that undue experimentation would be required to make applicants' compounds because applicants' compounds are not "structurally complex natural products".

As was also noted, Vippagunta emphasizes the ubiquity of solvates – stating that one third of pharmaceutically active substances are capable of forming crystalline hydrates:

3.1. Introduction to solvates and hydrates

It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates [68]. The water

Vippagunta p. 15, col. 1. Vippagunta's focus on the difficulty of predicting *the structure and stability* of solvates does not weigh heavily against the enablement of the present claims since the claims do not recite solvates of particular structure or stability. The applicants do not understand the Office's emphasis upon, and the supposed relevance of the issue of whether the exact structure of the solvates or hydrates can be predicted.

As was also noted above, predictability is only one of the factors to be considered in assessing enablement, unpredictability is not dispositive of the question of enablement. In the *Wands* case itself, making monoclonal antibodies was found to be *highly unpredictable* – much less predictable than forming solvates – but the court found the enablement requirement to be met *as a matter of law*, because of the routine methods of screening involved. As discussed below, as in *Wands*, routine methods of screening are available to identify solvates.

v. The State of the Art.

The Office cited Cocco as describing 4,5,6-substituted pyrimidines similar to compounds according to the rejected claims. Therefore, according to the Office, similar compounds structurally similar to those being claimed are known. The Office does not indicate that such compounds are particularly difficult to synthesize.

The applicants have also presented evidence that straightforward methods are available for the synthesis and screening of solvate and hydrate forms of pharmaceutical compounds. The methods are so routine that they can be implemented in high throughput form to discover solvates and hydrates of large numbers of compounds.

Therefore, the state of the art is clearly a factor which supports a finding of enablement.

vi. Amount of guidance provided by Applicant.

As indicated above, the applicants are perplexed by the Office's remarks stating that the applicants have "demonstrated within the application how to make triazolopyrimidines and pyrazolopyrimidines" but that the demonstration is insufficient to support the scope of the claims with respect to "R groups other than previously mentioned nor has applicant demonstrated any N-oxides, prodrugs, polymorphs or formulations. These cannot be simply willed into existence." As was noted above, these remarks do not appear to relate to the specification or claims of the present application.

The applicants respectfully submit, however, that the present application, in fact, provides a tremendous amount of guidance to the person skilled in the art for practicing the invention claimed herein. The specification provides over 200 pages of such guidance. For example, on pages 4 to 90, an exceedingly detailed account of compounds of the invention, including the embodiments and examples thereof, is provided. On pages 90 to 113, a detailed account of the utility of the compounds of the invention is provided, including guidance on how to formulate the compounds and suitable dosages. Then, on pages 113 to 126, numerous assays for evaluating the compounds are provided. On pages 127 to 222, methods of synthesizing **over 300 Examples** of compounds representative of the invention are provided. It is not seen that the Office has any basis to doubt the adequacy of the disclosure.

The extensive guidance provided by the applicants is clearly a factor which weighs in favor of a finding of enablement.

vii. Number of working examples.

As the applicants pointed out above, the present specification describes **over 300 working examples** of structurally diverse compounds within the scope of the invention, or structurally similar compouns, despite the fact that there is no requirement that applicants provide any working examples to satisfy the enablement requirement.

The large number of working examples provided by the applicants is again a factor weighing in favor of enablement.

viii. The Amount of Experimentation Needed to Make the Invention.

Applicants respectfully submit that, in view of the foregoing factors, the amount of experimentation required to carry out the claimed invention with the guidance provided by the 250 page specification and 300 working examples would be by no means undue. The specification describes methods of making compounds of the invention and screening them for relevant biological activity. Solvates of pharmaceutically active compounds are ubiquitous and methods of preparing and screening for solvates are straightforward and routine in the extreme.

In view of the foregoing factors and the high level of skill in the art, it would require no more than routine experimentation – synthesizing compounds and routine screening – to practice the invention of the rejected claims.

In view of the foregoing remarks, the applicants respectfully request that the rejection of claims under the enablement requirement of 35 U.S.C. § 112, first paragraph.

2. Rejection of Claims 1-3, 9, 11-61, 70, 72-76 and 78 under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 9, 11-61, 70, 72-76 and 78 were rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite. The applicants respectfully request reconsideration of the rejection.

The basis provided for the rejection is that certain terms that are said used in the claims are allegedly not clear. The allegedly unclear terms are "heteroaryl", "heterocycloalkyl" (and "terms containing contain these terms, such as 'heterobicycloalkyl,' 'heterobicycloalkylalkyl' or 'heterocycloalkylalkyl.'"), "carboxy" and "agonist compound."

MPEP 2173.02 explains that the focus of the enquiry for compliance with the requirement for definiteness "is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available." The Office "should allow claims which define the patentable subject matter with a *reasonable* degree of particularity and distinctness."

MPEP 2173.02 explains that:

The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a **reasonable degree of clarity and particularity**. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

- (A) The content of the particular application disclosure;
- (B) The teachings of the prior art; and
- (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The MPEP further emphasizes that "[s]ome latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire." MPEP 2173.02. "If upon review of a claim in its entirety, the examiner concludes that a rejection under 35 U.S.C. 112, second paragraph, is appropriate, such a rejection should be made and an analysis as to why the phrase(s) used in the claim is "vague and indefinite" should be included in the Office action." *Id.* "Examiners are encouraged to suggest claim language to applicants to improve the clarity or precision of the language used, but should not reject claims or insist on their own preferences if other modes of expression selected by applicants satisfy the statutory requirement." *Id.*

Applicants believe that the remarks provided below are sufficient to overcome the rejections made under 35 U.S.C. § 112, second paragraph and request that the rejection be withdrawn. If, however, after considering the remarks, the Examiner continues to be of the opinion that the claims are indefinite, the applicants would sincerely appreciate the Examiner's suggestions as to any improvements to the wording of the claims which the Examiner considers would improve their clarity.

a. **"Heteroaryl" and "Heterocycloalkyl"**

The Office Action states the following with regard to the terms "heteroaryl" and "heterocycloalkyl":

The scope of "heteroaryl" and "heterocycloalkyl" requires clarification. Applicants' examples in the specification are not limiting. Applicants have not defined these terms with reasonable clarity. See definitions on p.16 of the specification. Where applicants define terms with a special meaning, they must set out the special definition with "reasonable clarity, deliberateness and precision". ... These arguments also apply to definitions within the specification

which contain these terms, such as "heterobicycloalkyl," "heterobicycloalkylalkyl" or "heterocycloalkylalkyl."

i. **"Heteroaryl"**

Applicants disagree that the term "heteroaryl" is indefinite. The term is not defined, as the Office argues, by reference to examples. Rather the term is defined as one, two or three-ring aromatic ring system with at least one ring containing O, S, or N. On page 16, the specification states:

"The term "**“heteroaryl”**" denotes an aromatic ring system that may be a single ring, two fused rings or three fused rings containing carbons and at least one ring heteroatom selected from O, S and N.

Applicants do not see how this definition is considered to be indefinite.

ii. **"Heterocycloalkyl"**

The Office Action states that the use of the term "heterocycloalkyl" (and other terms containing it) is unclear, and that its definition given in the specification is also unclear.

Applicants respectfully point out that the terms "**"heterocycloalkyl"**", "**"heterobicycloalkyl"**", "**"heterobicycloalkylalkyl"**" or "**"heterocycloalkylalkyl"**" are not, in fact, used in the claims or used or defined in the specification of the present application. It would appear that the Office's remarks regarding these terms are referring to a different application from that which is presently under examination.

As such, it is respectfully submitted that there is no basis for the Office's assertion that the claims are rendered indefinite by virtue of including these terms.

b. **"Carboxy"**

Claim 56 was rejected because of its inclusion of the term "carboxy" which the Office states is considered an ambiguous term "in the chemical realm." It is stated that the term can either mean a carbonyl group or a carboxylic acid group. The applicants respectfully traverse the rejection.

Applicants respectfully submit that the term "carboxy" is not ambiguous because it is explicitly defined in the specification – on page 13 – as referring to a carboxylic acid group

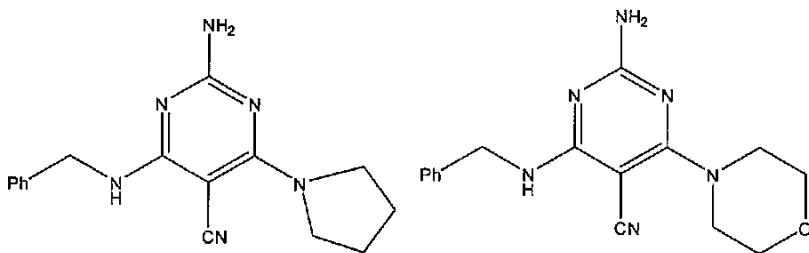
(-C(=O)OH). The specification states: "The term "carboxy" or "carboxyl" denotes the group -CO₂H; also referred to as a carboxylic acid." Furthermore, the Merriam Webster Online Dictionary does not, as the Office claims, defines "carboxyl" as referring to carbonyl group, but rather defines carboxy as being synonymous with "carboxyl", which in turn is defined as referring to a carboxylic acid group (-C(=O)OH), consistent with the definition in the specification and the Office's own cited definition from answers.com.

c. **"Agonist Compound"**

Claim 78 was rejected because of its recitation of the term "agonist compound", which was said to lack sufficient antecedent basis. The Office recommended amending the claim to recite the term "compound". The rejection is believed to be moot in view of the amendments made herein.

3. Rejections of Claims 1-3, 9, 12, 14-17, 32, 39, 41, 42 and 70 under 35 U.S.C. § 102(b) Over Cocco

Claims 1-3, 9, 12, 14-17, 32, 39, 41, 42 and 70 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Cocco, et. al., *J. Heterocyclic Chem.*, 2000, 37(4), 707-710 ("Cocco"). The reference is said to discuss the following compounds, which are said to correspond to a compound according to the rejected claims in which X and Y are N; W is a NH; V is a methylene group; Ar¹ is a phenyl ring; R¹ is an amino group; Z is a CN group; and the N-A-B-D ring is either a pyrrolidinyl ring or a morpholine ring:



The applicants request reconsideration of the rejection because the rejected claims do not read on the above-referenced compounds, at least because, in claim 1 as herein amended, V may not be methylene, D may not be oxygen, and R² may not be hydrogen.

IV. Information Disclosure Statement

Certain items of information were lined through in the Information Disclosure Statements attached to the Office Action. No reasons were given for the refusal to consider the information. Applicants are submitting herewith a new Information Disclosure Statement.

Applicants have made every effort to ensure that the Information Disclosure Statement complies with all the requirements of 37 CFR §§ 1.97 and 1.98. Should any omissions or deficiencies be noted, the Examiner is respectfully requested to provide the applicants with the opportunity to correct any deficiencies in accord with MPEP 609.05(a) (see Form Paragraph 6.51).

V. Conclusion

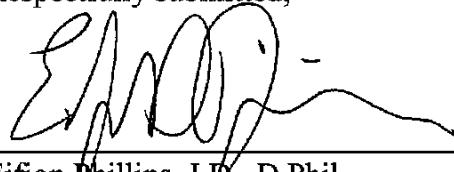
The applicants respectfully request reconsideration of the grounds of rejection in light of the amendments and the above comments. Further, early reconsideration and allowance of all pending claims is respectfully requested. It is believed that any pending objections and rejections have been addressed. If, at any time, it appears that a phone discussion would be helpful to resolve any outstanding issues, the undersigned would appreciate the opportunity to discuss any such issues at the Examiner's convenience.

Applicant : Robert M. Jones et al.
Serial No. : 10/541,657
Filed : March 3, 2006
Page : 66 of 66

Attorney's Docket No.: 20750-0007US1 / 034.US5.PCT

The Commissioner is hereby authorized to debit any fee due or credit any overpayment to Deposit Account No. 06-1050 quoting Attorney's Docket No. 20750-0007US1 / 034.US5.PCT. Even if not accompanied by an independent petition, this paper constitutes a Petition for an Extension of Time for an amount of time sufficient to extend the deadline and authorizes the Commissioner to debit the petition fee and any other charges or credits to Deposit Account No. 06-1050 referencing docket number Attorney's Docket No. 20750-0007US1 / 034.US5.PCT.

Respectfully submitted,



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Main Entry: **car·box·yl**

Pronunciation: \kär-'bäk-səl\

Function: *noun*

Etymology: International Scientific Vocabulary

Date: 1869

: a monovalent functional group or radical $-COOH$ typical of organic acids — called also *carboxyl group*

— **car·box·yl·ic** \kär-(.)bäk-'si-lik\ *adjective*

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Pronunciation Symbols

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Variant(s): *or carbox-*
Function: *combining form*
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